

# The Goodyear Tire & Rubber Company

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## COMMENTS ON NTP PROPOSAL FOR BUTADIENE TO BE DESIGNATED "KNOWN HUMAN CARCINOGEN"

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My name is Dr. Philip Leber from The Goodyear Tire & Rubber Company. Goodyear's economic interest in butadiene is related to the company's manufacture of butadiene copolymers which are used in numerous industrial, consumer, medical device, and food additive products. There are unquestioned regulatory, economic, and public implications for classification of butadiene as a "KNOWN HUMAN CARCINOGEN".

My comments rely in part on those of others who have or will address detailed toxicological and epidemiological issues relevant to the proposed action. It is my contention that a "KNOWN HUMAN CARCINOGEN" classification for butadiene is inconsistent with NTP's criteria as well as previous history for designation of other chemicals as "KNOWN HUMAN CARCINOGENS". What is the support for this statement?

First, the NTP term "KNOWN HUMAN CARCINOGEN". The stated criterion is that "there is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between the agent and human cancer". This designation applies only when the case for cause & effect is based on credible evidence, the link is unequivocal, and withstands all reasonable scientific debate.

Secondly, there is the issue of chemicals currently considered by NTP as "KNOWN HUMAN CARCINOGENS". Within the approximately 24 agents listed in the 7th Annual Report there are 7 organic chemicals in the industrial application category including 4-aminobiphenyl, benzene, benzidine, two chloromethyl ethers, 2-naphthylamine, and vinyl chloride. Three of these cause bladder cancer in workers at rates reported to be 10 times control levels; another study shows bladder cancers in over half of a population of 25 workers. Vinyl chloride induced the very rare angiosarcoma, and the chloromethyl ethers elevated the risk for lung cancer 10 times. Benzene induced an acute form of leukemia associated with blood toxicities in multiple studies. Yes, these chemicals are bona fide "KNOWN HUMAN CARCINOGENS" because the relationships

between exposures to discrete chemicals and specific human cancer endpoints have clearly been demonstrated.

Is Butadiene a "KNOWN HUMAN CARCINOGEN"? The three worker studies (Divine & Hartman; Ward et al; Delzell et al) cited in support of this contention provide contradictory data. The first two studies of monomer workers indicated an increase in the incidences of lymphohematopoietic cancers in workers who were employed in butadiene production. However, the most significant increase was in subgroups which averaged less than 5 years employment in monomer production. The small SMR value for the first study (SMR=1.5), the small size of the 2nd study (364 workers) combined with the fact that the degree of exposure was not correlated with tumor risks makes this evidence at most "suggestive".

Significantly, these two studies uncovered no increase in leukemia rates associated with monomer exposure in contrast to the finding reported for 15,600 styrene-butadiene workers in the Delzell study. This study reported an increased incidence of leukemia in association with SBR production jobs whereas lymphohematopoietic cancers were not elevated. Because many other chemicals besides butadiene are used within these operations, the authors concluded that "the results indicate that exposures in the SBR industry cause leukemia" which leaves open the possibility that other agents may act as confounders in human carcinogenesis. This is consistent with suggestions of Dr. Richard Irons at the 1997 summer Toxicology Forum that other agents are likely involved in leukemia etiology in SBR worker populations, and that leukemogenesis mechanisms for butadiene in mice do not apply to human disease.

At this time, unresolved issues include (a) is butadiene per se capable of inducing human cancer, (b) are confounders obligatory for the induction of human cancer by butadiene, and (c) what is the precise identity of butadiene-induced tumors in humans. These unresolved questions lead to the conclusion that this agent cannot now be considered a "KNOWN HUMAN CARCINOGEN".

The NTP's second cancer category termed "Reasonably anticipated to be carcinogens" is defined as "...limited evidence of carcinogenicity from studies in humans which indicates that causal interpretation is credible, but that alternative explanations such as chance, bias or confounding could not adequately be excluded". This statement describes most accurately the circumstance for butadiene. Until data have been developed that suggest a higher level of human evidence, butadiene should not be classified a "KNOWN HUMAN CARCINOGEN".